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14. **ABSTRACT**

We proposed to examine the novel hypothesis that the hCG genotype of a woman's offspring is associated with her breast cancer risk. Using the existing Metropolitan New York Registry (MNYR) resources, a case-control study was designed to examine the hypothesis whether first-born offspring's hCGβ 5 genotype (i.e., placental hCGβ 5 genotype during first full-term pregnancy) is associated with a woman's breast cancer risk. To date, the three tasks in the approved Statement of Work for year 1-3 have been accomplished. We have finished data analysis for the main results and we are in the process of manuscript preparation.

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INTRODUCTION:

It has long been known that both early age at first birth and total number of full-term pregnancies (FTPs) reduce breast cancer risk[1-5]. The underlying biology of this protection is yet to be clearly known. One or more of the hormonal changes during pregnancy are the logical candidates for this effect. Based on the published animal, human and epidemiological data, human chorionic gonadotropin (hCG), a glycoprotein hormone exclusively produced during pregnancy by the fetal part of placenta, has emerged as the most promising candidate[6;7]. The level of protection conferred by FTP may not be the same for all women, suggesting that there may be inherent variability in the protective effect across individuals. The hCG genes are well-known. Of the three trophoblastic hCG genes, hCGβ 5 is the most expressed gene in placenta, most highly conserved and the major contributor of hCG function during pregnancy [8;9]. The genotype of the fetal placenta is actually the genotype of the developing fetus. We proposed to examine the novel hypothesis that *the hCG genotype of a woman's offspring is associated with her breast cancer risk.* The data and biospecimens for this study are banked in the repository of the Metropolitan New York Registry (MNYR), one of six collaborating sites of the NCI funded Cooperative Family Registry for Breast Cancer Studies (CFRBCS). Since 1995, MNYR assembled 1,150 families with more than 3,500 individuals. Using the existing MNYR resources, a case-control study was designed to examine the hypothesis whether first-born offspring's hCGβ 5 genotype (i.e., placental hCGβ 5 genotype during first FTP) is associated with a woman's breast cancer risk. We proposed to evaluate our hypothesis by comparing the hCGβ 5 genes of first-born children of women with breast cancer (cases) and women without breast cancer (controls).

BODY:

This is the final report for year 3 of the study. We have aimed to finish tasks 7-8 listed below during year 3 in the approved Statement of Work. To date, majority of the tasks for year 1-3 have been accomplished, and we are in the process of manuscript writing.

Year 1

Task 1: Identification of 1,106 eligible breast cancer cases and unaffected controls and their first-born children in MNYR database who are eligible for the study.
Task 2: Cleaning and editing of the questionnaire and family history data on the eligible study participants.
Task 3: Obtaining the DNA samples from the MNYR biospecimen bank on the 1,106 eligible study participants.

Year 2

Task 4: Genotyping 1,106 samples for the four SNPs in hCGβ 5 gene using fluorescent polarization technique in 96 micro-well plate format.
Task 5: Cleaning and editing of the laboratory data
Task 6: Combining questionnaire and family history data with the laboratory data

Year 3

Task 7: Conducting statistical analysis to examine the association between offspring's hCGβ 5 genotype and breast cancer risk adjusting for potential confounders.
Task 8: Dissemination of study findings, including report writing, presentation in the AACR or ASHG Annual Meetings and preparation of manuscripts for publication.

For the proposed study, a separate database specific for this project has been created containing all relevant data. Cases and controls of breast Cancer and their older offspring with available blood samples

were included in the proposed study. DNA samples of 297 cases and 237 controls and their older offspring were genotyped using fluorescent polarization technique to date for CSH1 rs2955245, CGB5 rs7260002, and CGB5 rs7246045 gene. Standard data cleaning and editing have been performed on these data to ensure that the case-control status.

To test the hypothesis that offspring's placental hormonal genotype is associated with risk of breast cancer in mothers, data were analyzed using unconditional logistic regression. We estimated adjusted odds ratios for breast cancer. Odds ratios were adjusted for race, age, ever HRT use, current HRT use, ever OC use, and number of live children of mother.

Table 1 shows the relationship between CGB5 rs7260002 genotypes and maternal breast cancer status. We analyzed the data under three genetic models. Under both additive and dominant models, data suggested that offspring with C allele were more likely to have a mother with breast cancer. However, the elevated risk is not statistically significant.

Table 2 shows the relationship between CSH1 rs2955245, CGB5 rs7246045 genotypes and maternal breast cancer status. For CGB5 rs7246045, we analyzed the data under dominant model, since the variant allele is rare. We did not observe an apparent association between offspring's CGB5 rs7246045 genotypes and maternal breast cancer. For CSH1 rs2955245, we analyzed the data under three genetic models. Under both additive and recessive models, data suggested that offspring with AA genotype were more likely to have a mother with breast cancer. However, the elevated risk is not statistically significant.

Table 3 shows the effect of joint exposure to offspring's CGB5 rs7260002, CSH1 rs2955245 genes and maternal later age of giving first birth on risk of maternal breast cancer risk. Dichotomized categories for maternal later age of giving first birth was created based on median value in the data. For CGB5 rs7260002, we did not find that the effects of CGB5 rs7260002 C allele of offspring's and maternal later age of giving first birth were additive or beyond additive. On the other hand, for CSH1 rs2955245, elevated breast cancer risk was only elevated among those whose offspring with CSH1 rs2955245 A allele and who gave first birth later, suggesting the effects of the two exposures were additive.

Table 1. Association Between Maternal Breast Cancer and the CGB5 & CSH1 Promoter Variant Allele(s) of the Oldest Offspring

Gene/genotype of the older offspring	Maternal breast cancer status		Adjusted OR for mother's breast cancer , 95% CI [1]
	Case	Control	
CGB5 rs7260002			
AA	106	96	1.00
CA	139	105	1.19 (0.80-1.77)
CC	48	34	1.22 (0.70-2.12)
AA	106	96	1.00
CA/ CC	187	139	1.19 (0.82-1.74)
AA /CA	245	201	1.00
CC	48	34	1.11 (0.67-1.85)

[1] ORs were adjusted for race, age, ever HRT use, current HRT use, ever OC use, and number of live children of mothers.

Table 2. Association between maternal breast cancer and genotypes of the oldest offspring

Gene/genotype of the older offspring	Maternal breast cancer status		Adjusted OR for mother's breast cancer , 95% CI [1]
	Case	Control	
CGB5 rs7246045			
TT	289	228	1.00
GT	7	9	0.67 (0.23-1.95)

CSH1 rs2955245			
GG	154	127	1.00
GA	112	94	0.97 (0.66-1.42)
AA	22	14	1.60 (0.73-3.48)
GG	154	127	1.00
GA/AA	134	108	1.04 (0.72-1.50)
GG/GA	266	221	1.00
AA	22	14	1.62 (0.76-3.48)

[1] ORs were adjusted for race, age, ever HRT use, current HRT use, ever OC use, and number of live children of mothers.

Table 3. Risk of Maternal Breast Cancer in Relation to Her Age at First Birth and the CGB5 & CSH1 Promoter Variant Allele(s) of Her Oldest Offspring

Gene/genotype of the oldest offspring	Age at first birth of mothers. Median = 25	Adjusted OR for mother's breast cancer , 95% CI [1]
CGB5 rs7260002		
AA	<25	1.00
CA/CC	<25	**2.20 (1.27-3.82)**
AA	25+	**2.66 (1.47-4.79)**
CA/CC	25+	**2.21 (1.31-3.74)**
CSH1 rs2955245		
GG	<25	1.00
GA/AA	<25	1.40 (0.79-2.49)
GG	25+	1.45 (0.87-2.45)
GA/AA	25+	**2.31 (1.35-3.95)**

[1] ORs were adjusted for race, age, ever HRT use, current HRT use, ever OC use, and number of live children of mothers.

KEY RESEARCH ACCOMPLISHMENTS:

We examined the novel hypothesis that the hCG genotype of a woman's offspring is associated with her breast cancer risk and concluded the following:

Offspring's CSH1 rs2955245 A allele and CGB5 rs7260002 C allele may be positively associated with maternal breast cancer risk.

Relationship between offspring's CGB5 rs7246045 gene and maternal breast cancer risk is not clear.

We also found that women whose offspring with CSH1 rs2955245 A allele and who gave first birth later had a significant elevated risk of breast cancer, compared to those whose offspring with CSH1 rs2955245 G allele and who gave first birth earlier. This findings suggested the effects of later age of giving first birth and placenta CSH1 rs2955245 G allele may be additive.

REPORTABLE OUTCOMES:

Abstracts and presentations:

Chen Y, Kibriya M, Whittemore A, Senie R, Santella R, and Ahsan H. Offspring's and father's HCG genotype and risk of breast cancer in mother. Presented at the fourth Era of Hope meeting for the Department of Defense (DOD) Breast Cancer Research Program (BCRP), June 8-11, 2005, Philadelphia, Pennsylvania.

CONCLUSIONS:

This is the first study to evaluate hCG genotype of a woman's offspring and her breast cancer risk. In conclusion, preliminary analysis suggested offspring's CSH1 rs2955245 A allele and CGB5 rs7260002 C allele may be positively associated with maternal breast cancer risk. Relationship between offspring's CGB5 rs7246045 gene and maternal breast cancer risk is not clear. In addition, data also suggested interaction between these offspring's genes and maternal age at first birth on maternal breast cancer risk. Further analysis is in progress and results need confirmation in future studies. Larger sample size is needed for future studies. Additionally, future studies should consider effects of other maternal hormone-related lifestyle factors in the analyses.

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APPENDICES:

Not applicable